Testing of a novel Valsalva Assist Device with Supine and Modified Positions in healthy volunteers

Izzy FitzGerald[1], Professor Paul Ewings[2*], Dr Iain Lang[2], Professor Andy Appelboam[3*]

1: University of Exeter Medical School, Exeter, UK, if223@exeter.ac.uk, 07515688294,
2: University of Exeter, Exeter, UK
3: Academic Department of Emergency Medicine, Royal Devon and Exeter Foundation Trust, Barrack Road, Exeter, EX2, 07758842330 (Corresponding Author)

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Izzy FitzGerald[1], Professor Paul Ewings[2*], Dr Iain Lang[2], Professor Andy Appelboam[3*]

1: University of Exeter Medical School
2: University of Exeter
3: Academic Department of Emergency Medicine, Royal Devon and Exeter Foundation Trust

Statement of Contribution

IF recruited the participants, ran the study and wrote the first draft of the manuscript. PE advised on study design, conduced the statistical analysis and reviewed the manuscript drafts. IL co-supervised IF, advised on the project and reviewed the manuscript. AA conceived the idea for the study, co-supervised IF, reviewed and revised the manuscript and acts as guarantor. The project was part of IF's masters by research (MbyRes) project at the University of Exeter and was also submitted to the RCEM undergraduate research competition.

Abstract

Background The Valsalva Manoeuvre (VM) is used to treat Supraventricular tachycardia (SVT) by inducing a vagal response (drop in heart rate). Body position and how the VM strain is generated may affect the efficacy of this treatment. There is debate as to the best position in which to carry out the VM and how the strain should be delivered in practice. We aimed to compare vagal responses induced with supine and modified VMs using strains delivered with a standardised manometer or novel Valsalva Assist Device (VAD), a simple device to provide resistance to exhalation, in healthy volunteers.

Methods We did a repeated measures randomised trial of four VMs (2 Supine VM and 2 modified VM's) in healthy adult volunteers with strains delivered using an adapted sphygmomanometer (manometer) or a VAD. Changes in heart rate were monitored and compared between the techniques and devices. The pressure and duration of VM strains achieved with the VAD and manometer and any adverse events were also compared. The trial was conducted at the Royal Devon & Exeter

Hospital over a four month period (November to February 2018), was registered with ClinicalTrials.gov (NCT03298880) and approved by the University of Exeter Medical School Research ethics committee.

Results 75 healthy participants aged 19-55 were recruited over a four month period. A mixed-effects linear regression was completed showing the modified VM resulted in a significantly greater drop in heart rate of 3.8 bpm compared to the supine VM (p=0.002, CI **2.2-5.4**). VM strains produced by the VAD were of a similar pressure but of slightly shorter duration and resulted in a statistically smaller drop in heart rate of 1.9 bpm (p=0.01, CI 0.4-3.4) compared to the manometer.

Conclusions Modified VM was associated with a greater drop in heart rate than a supine VM without an increase in adverse events in healthy volunteers. The Valsalva Assist Device can be used to safely generate the recommended VM strain pressure, but produced a smaller drop in heart rate compared to a manometer and requires modification to enable the recommended strain duration to be achieved consistently.

Introduction

The Valsalva manoeuvre (VM) is an internationally recommended first-line treatment for haemodynamically stable supraventricular tachycardia (SVT).[1] The VM involves an exhalation strain against resistance which causes a reflex slowing of heart rate mediated by the vagus nerve. The highest VM cardioversion rates in emergency medicine practice to date have been achieved in a study (REVERT) using a postural modification and a manometer delivered strain compared with semi-recumbent controls. In this study, intervention patients with SVT undertook Valsalva strains using an adapted sphygmomanometer, blowing for 15 seconds at 40mmHg in a semi-recumbent position before immediate supine repositioning with passive leg raise at the end of the strain.[2]

However there is debate whether this modification has any advantage over a purely supine VM which is associated with a greater vagal response in healthy volunteers compared to sitting and Trendelenberg position VMs [3] and may reduce the risk of adverse events.[4] Adapted manual sphygmomanometers are also not routinely

available for VMs carried out in normal practice and whilst surrogates such as blowing on empty syringes are commonly used, they have been shown to be unreliable.[5]

A simple hand held Valsalva Assist Device (VAD) has been developed to provide 40mmHg resistance to exhalation and is available as a CE marked device ('Valse-Valve' Valsalva Assist Device, Meditech Systems Limited, Shrublands Estate, Sherstock, Shaftesbury, Dorset, SP7 9PT. See figure 1). This device has a mouth piece, a pressure indicator and an air leak to prevent mouth pressure only generated strains (pressure not transmitted to the thorax). However it has not been tested against a sphygmomanometer in healthy volunteers or in the postures that might be used in clinical practice. Such a device used in clinical practice, would be advantageous to control and standardise strains and could also carry clear instructions for the recommended VM posture and strain duration.

We conducted a repeated measures trial to compare the vagal responses (drop in heart rate) and strain characteristics achieved by healthy volunteers performing VMs in both supine and modified positions using the VAD and adapted sphygmomanometer ('manometer'). Our objectives were to compare the vagal response to modified and supine VMs and to assess the performance of the VAD.

Methods

Participants:

The study was approved by the University of Exeter ethics committee and registered with ClinicalTrial.gov (NCT03298880) prior to commencement of recruitment. Healthy adult volunteers (18-60 years) from University of Exeter or Royal Devon & Exeter Hospital NHS Foundation Trust staff were invited to take part through posters and social media. All participants were screened for eligibility (figure 2) and provided informed written consent prior to participation.

Screening involved physical examination, including observations of pulse, oxygen saturations, respiratory rate and blood pressure and the recording of a 12 lead ECG.

Testing was conducted in the clinical research facility (CRF) of the Royal Devon & Exeter Hospital, according to a strict trial protocol.

Sample Size Calculations: Previous volunteer studies have suggested a difference of at least 3 beats per minute as an important difference between techniques.[3] We therefore powered our study to detect a difference of 4 beats/min, also taking into account informal pilot work suggesting at least this level of difference might be expected between techniques whilst ensuring a reasonable size study population and appropriately narrow confidence intervals. Calculations were based on a simple paired t-test using the standard deviations reported by G Smith et al in a similar study (about 12 for both individual measures and for differences between measures). With these parameters, a sample size of at least 73 participants would provide 80% power at the 5% level of significance. We planned to recruit a total of 75 participants in case of unexpected drop outs or device failure.

Procedures:

We conducted a randomised repeated measures trial between November 1, 2017 and February 5, 2018 with participants undergoing a total of four VMs of the following variations in random order, stratified by all possible orders:

Study Valsalva Manoeuvre Interventions:

1. *Supine VM using manometer.* Supine Valsalva strain using a manometer visible to the participant with a target of 40mmHg for 15 seconds.
2. *Modified VM using manometer.* Semi-recumbent (at 45 degrees) Valsalva strain using a manometer visible to the participant with a target of 40mmHg for 15 seconds followed by supine positioning and passive 45 degree leg lift immediately at the end of the strain for a further 15 seconds.
3. *Supine VM using device.* Supine Valsalva strain using the device connected to manometer invisible to the participant but visible to a researcher for 15 seconds.
4. *Modified VM using device.* Semi-recumbent (at 45 degrees) Valsalva strain using the device connected to manometer invisible to the participant but visible to a researcher for 15 seconds followed by supine positioning and passive 45 degree leg lift immediately at the end of the strain for a further 15 seconds.

All testing was performed on a standard hospital trolley with a manually adjustable back rest. A 45 degree angle template guide was used to ensure consistent back rest and leg elevation angles. Participants lay at rest for 5 minutes prior to testing to ensure baseline resting heart rate was achieved. Participants were read clear, standardised instructions before each manoeuvre and target pressures were marked on the manometer and device gauges. No practices were allowed. A new device and a new 92cm length of green oxygen bubble tubing, for the manometer, were used for each participant.

A stop watch was used to time all procedures and was visible to participants and researchers. Participants were instructed to stop blowing after the 15 second strain but no other encouragement or instruction was allowed. For safety, participants were not allowed to blow more than 50mmHg, as measured on the manometer, whether using the manometer or device to generate the strain. It was planned that in event of device malfunction (ie it provides no resistance or resistance is greater than 50mmHg), the VM would be abandoned and the malfunction recorded as an adverse incident. The particular manoeuvre would then be restarted using a new device, if the participant was happy to continue.

There was a three minute washout period between strains including two minutes rest after any change in posture. Continuous 3 lead ECG monitoring on the same, previously calibrated, print enabled defibrillator (Smart Biphasic AED, Philips Heartstart XL) was used to assess heart rate during the manoeuvre. Standard ECG rhythm strip traces (25mm/second) were printed for 45 seconds (15 seconds before, during and 15 seconds after each VM). They were marked at the onset of each Valsalva strain, labelled with a code and subsequently analysed in batches, blind to technique according to the method described by G Smith et al.[3] These traces were second read by another researcher, who was not part of the study team nor present at testing and also blind to allocation.

Pre-manoeuvre heart rates were determined by calculating the mean R-R interval of the 10 beats preceding each manoeuvre before converting it to heart rate in beats/minute ((25/mean R-R interval)x60). The lowest post manoeuvre heat rate was determined by measuring and recording the longest R-R interval during and up to 15

seconds post manoeuvre, converted to a heart rate in beats per minute ((25/longest R-R interval)x60). The difference between the pre and post manoeuvre heat rate indicated the degree of vagal tone or slowing of heart rate induced by each manoeuvre. Where there was disagreement in ECG measurements between the two readers, the mean of the two figures was taken. The peak sustained strain pressures achieved, as observed on the manometer and duration of longest strain attempt during all VMs were also recorded on a standard report card.

Participants were monitored for any adverse events. Participants who felt unwell or who developed any significant or persistent ECG abnormalities were immediately withdrawn from further testing and appropriate further clinical assessment arranged. All adverse events were recorded, graded and reported according to Good Clinical Practice guidelines.

Statistical Analysis:

The heart rates measured under each of the four testing scenarios were summarised appropriately, e.g. mean and SD, with the expectation that heart rate would be approximately normally distributed. The following comparisons of drop in heart rate were planned:

1. Supine VM vs modified VM (recognising that this comparison may or may not be different according to how the strain was generated – manometer or device)

2. Manometer vs device (recognising that this comparison may or may not be different according to the posture used – supine or modified)

Analysis was based on mixed effects linear regression (with appropriate prior assessment of assumptions, eg Normality), assessing post-VM heart rate with individual as a random effect, and posture (supine/modified) and strain method (manometer/device) as fixed effects. An interaction term (posture x strain method) was examined to consider whether there was any evidence of a differential effect (of strain method according to posture, or equivalently posture according to strain method), but was planned to be dropped from the model if $p>0.1$ (no evidence of interaction). If the interaction term was to be retained then comparison 1 between postures would be presented separately by strain method, and comparison 2

between strain methods would be presented separately by posture type; otherwise the two comparisons would be presented overall.

Two versions of the model were used, one adjusting for pre-VM heart rate as a covariate, the other not doing so. The pre-VM heart rate was measured having assumed the relevant starting position for the next manoeuvre, and was (unsurprisingly) lower for the supine manoeuvres than the modified versions, which start in a semi-recumbent position. Hence these pre-VM heart rates are not true baselines comparable across the four scenarios. Moreover, since all four manoeuvres were undertaken by each person (hence essentially comparing results "within" person), the starting heart rate adds little to statistical efficiency.

Results

80 volunteers were screened and 5 were excluded (heart murmurs (2), ECG abnormalities (2) and participant on medication (1)). 75 healthy participants aged 19-55 years (mean 26) underwent trial VMs. 45 (60%) were female. All participants completed all four VMs and there was no missing data. There was one device failure where the pressure observed by manometer was 60mmHg while the device was showing a pressure 40mmHg. This attempt was abandoned and redone with a new device and reported as an adverse event as described in the methods.

Agreement of readers

For the traces analysed for 10 beats prior to the manoeuvre, the two readers had very good agreement for measuring the relevant interval: they both reported overall means of 180.8mm, with 71% of the 300 readings being identical. 99% of readings were within 1mm and the (single) worst discepancy was 2.5mm. For the post-manoeuvre readings of the longest R-R interval, the two readers both recorded overall means of 27.8mm, with 80% of readings identical and 100% within 1mm. As agreement of the trace readings were very good (intraclass correlation 0.999 or higher), a simple average of the two readings was subsequently used in the analyses.

Effects on Heart Rate

All manoeuvres were associated with a substantial drop in heart rate. Mean heart rates observed for the four VMs are summarised in table 1 together with Valsalva ratios (highest heart rate/lowest heart rate recorded during the VM)

Table 1. Mean heart rate (sd) with study Valsalva Manoeuvres

Study VM	Pre-VM HR	Post-VM HR	Difference	VR
Supine with manometer	**82.8 (15.8)**	**55.7 (9.4)**	**27.1 (12.4)**	**1.49**
Modified with manometer	**88.1 (14.4)**	**53.7 (10.9)**	**34.4 (15.2)**	**1.64**
Supine with VAD	**83.1 (14.7)**	**58.0 (10.0)**	**25.1 (9.3)**	**1.43**
Modified with VAD	**88.4 (15.6)**	**55.4 (9.7)**	**32.9 (14.3)**	**1.60**
All supine	**83.0**	**56.9**	**26.1**	**1.47**
All modified	**88.3**	**54.6**	**33.7**	**1.66**
All manometer	**85.5**	**54.7**	**30.7**	**1.59**
All VAD	**85.8**	**56.7**	**29.10**	**1.53**

n= 75

VR: Valsalva Ratio (pre-VM HR/post-VM HR)

The table also shows the “marginal” results for all supine manoeuvres (combining manometer and device results); all modified manoeuvres (similarly), all manometer use (combining supine and modified manoeuvres) and all VAD use (similarly).

These unadjusted means in table 1 suggest that the modified manoeuvre was associated with a greater reduction in heart rate than the supine manoeuvre, a difference of about 8 bpm. Moreover this difference is consistent across strain methods, with a similar difference whether the manometer or device is used. The table also suggests a small difference between the two strain methods, with a slightly larger reduction in heart rate for the manometer compared with the VAD, again with consistency across the two postures used.

The mixed effects regression (including pre-VM heart rate as a covariate) resulted in a small interaction (strain method x posture of VM) with a p-value of 0.70, hence was

dropped as planned. The resulting model then showed a significant effect for VM posture used, with the modified version reducing heart rate by 3.8 bpm more than the supine version (95% confidence interval 2.2 to 5.4; p<0.001). The strain method also showed a significant effect (albeit weaker), with the manometer reducing heart rate by 1.9 bpm more than the VAD (95% CI 0.4 to 3.4; p=0.01). Shown in table 2

Table 2. Adjusted differences in fall of heart rate between postures and strain methods using mixed effects regression to adjusting for baseline (pre-VM) heart rate

Comparison	Difference in bpm (95%CI)	P value
Supine v Modified VM	**3.8 (2.2-5.4)***	**P<0.001**
VAD v Manometer	**1.9 (0.4-3.4)****	**P=0.01**

***Lower post VM HR with modified VM**

****Lower post VM HR with manometer**

Repeating the regression without the pre-VM heart rate as a covariate produced similar results: a small non-significant interaction (p=0.69), and significant benefits for the modified posture (2.3 bpm, 95% CI 0.8 to 3.8; p=0.003) and manometer (2.0 bpm, 95% CI 0.5 to 3.5; p=0.01).

Strain Characteristics (See table 3)

The mean strain pressures delivered by manometer and VAD were similar (39.96 vs 42.46 mmHg) but manometer was more precise with 97% of participants straining between 35-45mmHg compared to 75% when using the VAD. The use of VAD was also associated with significantly shorter total duration of strain and anecdotally was due to subjects running out of breath. This was particularly evident in females with only about a third of female participants achieving a full 15 second strain with the device compared to 95% of males (data not shown).

Table 3. Mean Pressure and Strain Duration Characteristics

Strain Method	Mean Peak Pressure (mmHg)	Proportion in35-	Mean Duration (secs)

		45mmHg range (%)	
Manometer	**39.96**	**97**	**14.91**
VAD	**42.46**	**745**	**13.70**

Adverse Events: (See table 4)

34 (11%) of the 300 VM undertaken were associated with symptoms reported during the attempts. All of these were transient and did not prevent completion of VMs and were similar between the four different VM under investigation. The most common side effect was a headache and light-headedness. No serious adverse events were recorded.

Table 4. Recorded adverse events by allocation

	The Modified VM		The Supine VM	
	VAD	Manometer	VAD	Manometer
Lightheaded	3	2	1	1
Tingling lips	1			1
Ectopic	1			
Rib strain	1			
Head rush				1
Unable to blow into tube				1
Headache	1	6	4	6
Vision changes				2
Chest discomfort	1			
Device failure			1	
Totals	8/150	8/150	6/150	12/150
Totals Modified and Supine	16/150		18/150	

Discussion

Our results demonstrate the physiological advantage of the described modified Valsalva over a purely supine VM. This postural modification was associated with a greater vagal response, shown by the absolute and relative drop in heart rate compared to the supine VM. Despite supine positioning being associated with a lower initial heart rate (likely because of initial increased vagal tone), the exaggerated effects on venous return resulting from semi-recumbent position in the strain phase and leg elevation in the supine relaxation phase (Valsalva stage 3) resulted in more intense vagal stimulation overall with the modified VM.

Previous work has suggested that vagal techniques associated with a greater drop in heart rate and so larger Valsalva ratio, are correlated with a greater chance of SVT being terminated when that vagal manoeuvre is used to treat this arrhythmia.[6] So, although caution must be employed in extrapolating volunteer studies, demonstration of a significantly greater drop in heart rate with the modified VM in this study, is consistent with the efficacy of this postural modification in clinical trials.[2,7] and benefits of a modified VM over a purely supine technique.

Although straining in upright postures is in theory associated with a greater drop in blood pressure and an increased risk of syncope during straining [7], this complication was not seen in our study which used a controlled and defined strain and is consistent with our experience of the modified VM in clinical practise and trials. There were no serious adverse events and the number of non-serious adverse events was similar between the two different posture groups. We believe this study therefore further supports the case for routine use of a modified VM as described, over a supine VM.

Overall, VMs with VAD generated strains resulted in a meaningful fall in heart rate of 29bpm. This is greater than that seen in similar volunteer studies using a manometer [3, 8] The VAD however, did not perform quite as well as the manometer in terms of vagal response in our study. Although the difference in drop of mean heart rate between these strain methods just reached statistical significance, it was less than our previously stated clinically meaningful difference of 4 bpm (which was also excluded from the 95% confidence interval) and it is debateable whether this small difference. would affect cardioversion rates if it were replicated in clinical practice

The device produced a similar mean pressure of strain. Although the variation of pressures was greater than with manometer, this was within a clinically appropriate range and considerably better than that seen with use of a syringe.[4] The VAD however, was associated with significantly shorter strain durations than strains utilizing the manometer. This was almost certainly due to the pre-designed air leak which was probably a little too large for most volunteers compared to the manometer which is a sealed system with no leak. Shorter durations of strain were seen most with VAD delivered strains by female participants. Female sex is associated with a physiologically lower functional residual lung capacity and supports the theory that the device leak was the cause for the reduced strain duration observed with the VAD. This degree of leak and shorter duration of VM strain might account for the devices marginally reduced effect on heart rate. This has been fed back to the manufacturer to consider refinements to their design. There was no significant difference but a trend towards a lower number of adverse events in the VAD group. Further study could reassess performance of such device modifications and compare it again to the manometer or to the syringe, as the most commonly used alternative in practice.

We conducted our study on mainly young, healthy volunteers with a slight preponderance to females. This is the demographic of many patients with SVT however there is a second peak of incidence in older age, often in patients with associated co-morbidities and so consideration should also be given to repeating this study and assessing VAD performance in the older population.

Finally, findings from this volunteer study using the VAD should not be used alone in changing the care of patients with SVT. Other work will be needed to assess the performance of such devices in clinical practice A feasibility trial is currently underway to look at use of the VAD (after modifications) by paramedics in the South West of England to treat patients with SVT (EVADE Study, NCT03514628).

Conclusions

This study indicates that a modified VM results in a greater vagal response than a standard supine VM with no increase in adverse effects when used with a controlled strain in healthy volunteers. Our findings give support for the physiological advantage of this specific manoeuvre over a purely supine VM.

We have also shown a simple hand held device can be used to generate recommended VM strain pressures but its use in volunteers resulted in shorter strain durations and a slightly smaller drop in heart rate compared to a modified sphygmomanometer. Refinements to this device may improve its function further and allow it to be assessed in clinical practice to treat SVT.

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Clinical Trial registration - ClinicalTrial.gov (NCT03298880)

Ethics Approval

This study was approved by the University of Exeter Medical School research committee. Location – The Research, Innovation, Learning and Development Building, Royal Devon and Exeter Hospital, Barrack Road, Exeter, EX2 5DW.

Funding Statement

The project was supported by the University of Exeter Medical school as part of a master by research project (IF) and the academic department of Emergency Medicine. Devices were supplied by Meditech Systems Limited and purchased jointly by the academic department of Emergency Medicine and the Academic Health Science Network (SW).

Competing Interest Statement

The Royal Devon & Exeter Hospital NHS Foundation Trust introduced the concept of the Valsalva Assist Device to Meditech Systems Limited, advised on refinements to the device and as such, the trust has a royalty agreement on future sales of the device. None of the research team have received or currently stand to gain personal financial benefit from Meditech, are shareholders or have any direct financial interest in the company. Meditech had no involvement in the funding, design, analysis or interpretation of the study nor any role in the publication of its findings.